Identifying subgroups of community-dwelling older-adults and their prospective associations with long-term knee osteoarthritis outcomes

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ABSTRACT

Objectives: To identify subgroups of community-dwelling older-adults and to assess their longitudinal association with long-term osteoarthritis(OA) outcomes.

Methods: 1046 older-adults aged 50–80 years were studied. At baseline, body mass index (BMI), pedometer-measured ambulatory activity(AA), Western Ontario and McMaster Universities Osteoarthritis Index(WOMAC) determined knee pain and information on comorbidities were obtained. Tibial cartilage volume and bone-marrow lesions(BMLs) were assessed using MRI at baseline and 10 years and total knee replacements(TKR) by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry. Latent class analysis was used to determine participant subgroups, considering baseline BMI, AA, pain and comorbidities and linear mixed-effects or log-binomial models were used to assess the associations.

Results: Three subgroups/classes were identified: subgroup 1 (43%): Normal/overweight participants with higher AA, lower pain and lower comorbidities; subgroup 2 (32%): Overweight participants with lower AA, mild pain and higher comorbidities; subgroup 3 (25%): Obese participants with lower AA, mild pain and higher comorbidities. Subgroup 3 had greater cartilage volume loss (β:-60.56mm^3, 95%CI:-105.91,-15.21) and a higher risk of TKR (RR:3.19, 95%CI:1.75,5.81), compared to subgroup 1. Subgroup 2 was not associated with cartilage volume change (β:13.06mm^3, 95%CI:-30.87,57.00) or risk of TKR (RR:1.16, 95%CI:0.56,2.36), compared to subgroup 1. Subgroup membership was not associated with worsening BMLs.

Conclusions: Our findings suggest the existence of homogeneous subgroups of participants and support the utility of identifying patterns of characteristics/risk factors that may cluster together and using them to identify subgroups of people who may be at a higher risk of developing and/or progressing OA.

Keywords: osteoarthritis, latent-class analysis, cartilage volume, bone-marrow lesions, total knee replacement.

Key messages

- Complex interplay among characteristics/factors leads to conflicting evidence between ambulatory activity and knee osteoarthritis.

- Distinct subgroups are identifiable based on ambulatory activity, body mass index, knee pain and comorbidities.

- Identifying subgroups can be used to determine those who are at risk of developing/progressing osteoarthritis.

INTRODUCTION

Knee Osteoarthritis (OA) is a complex disease with multiple contributing factors[1]. The rates of incident knee OA and the need for total knee replacements (TKR) have been increasing steadily[2]. Hence, identification of characteristics/risk factors for the onset and progression of knee OA will aid in designing better preventative and management strategies.

Traditionally, epidemiological studies have investigated individual characteristics/risk factors in isolation, and their associations with knee OA[3, 4]. While there have been clear associations identified between some factors such as obesity and knee OA[5], the association of ambulatory activity (AA) with knee OA has been conflicting[6]. One important reason for this inconsistency could be the heterogeneity of the population characteristics and the complex interplay between characteristics[7]. Hence, acknowledging the existence of certain patterns of characteristics/risk factors leading to subgrouping may help to improve the overall understanding of OA[8, 9]. Accordingly, it may prove more valuable to examine AA as one characteristic that clusters with other characteristics[10]; i.e. to identify relatively homogenous subgroups of participants with similar characteristics which includes AA and to examine the relationship between the subgroups and OA outcomes.

Identification of such subgroups can relay important information on the aetiology of the disease[11] and will assist in designing better preventative strategies[12]. In identifying subgroups, it is further important to consider modifiable characteristics rather than non-modifiable characteristics (e.g.: age, sex) in order to improve the usefulness of classification in clinical practice and in epidemiological studies[9, 13]. Factors/characteristics such as body mass index (BMI)[14] and comorbidities[15] are suggested to be correlated with AA in older-

adults. In addition to these factors/characteristics, pain in OA may also affect the AA levels in people as the AA levels may be adjusted in order to reduce the pain experienced[10, 16, 17]. Hence, these modifiable factors could be useful in identifying naturally occurring subgroups in populations.

We therefore hypothesized that there are distinct subgroups of participants with similar characteristics, based on AA, knee pain, BMI and comorbidities which are associated with the onset and progression of knee OA. The objectives of this study, thus, were to identify subgroups of individuals using a multi-dimensional approach and to investigate the longitudinal association of these subgroups with tibial cartilage volume change, worsening bone-marrow lesions (BMLs) and TKR in a population of community-dwelling older-adults.

MATERIALS AND METHODS

Study population

This study was based on Tasmanian Older Adult Cohort Study (TASOAC). TASOAC is a prospective population-based study aimed at examining the incidence and progression of OA. The participants between 50-80 years were randomly selected with an equal number of men and women from the community in Southern Tasmania (population 229,000) using the electoral roll. Electoral rolls represent the most complete population information available in Australia because voting is compulsory in federal and state elections. The sample was stratified by sex to provide equal numbers of men and women, and equal distribution was drawn from urban and rural areas. As TASOAC was designed to examine community-dwelling older adults, institutionalised older adults were excluded. Participants were also excluded if they had contraindications to Magnetic Resonance Imaging **(**MRI). Data collection was undertaken at baseline (n=1099) between March 2002 and September 2004 and at 10 years. Of the initially eligible participants contacted (1,904), 1,099 were enrolled in the study (57% response rate). The research was conducted in compliance with the Helsinki Declaration. Ethical approval was granted by the Southern Tasmanian Health and Medical Human Research Ethics Committee. Written informed consent was obtained from all participants.

Magnetic Resonance Imaging

A 1.5T MRI of the right knee was performed at baseline and 10 years, in the sagittal plane on a Picker apparatus (Ohio, USA) and a Siemens apparatus (Espree, Pennsylvania, USA). The image sequence is explained elsewhere[18]. Briefly: (1) T1-weighted fat saturation three–

dimensional gradient-recalled acquisition in the steady state, (2) T2-weighted fat saturation two-dimensional fast spin echo.

Cartilage volume (mm^3)

A trained reader assessed the cartilage volume on T1-weighted MRIs using OsiriX software (University of Geneva, Geneva, Switzerland)[19]. The coefficient of variation for intra-observer repeatability ranged from 2.1–2.2%[19]. Medial tibial and lateral tibial cartilage volumes were measured. Total tibial cartilage volume was calculated as medial + lateral tibial cartilage volumes.

Cartilage volume measurements were conducted with the baseline and 10-year MRIs paired, with the chronological order known for participants who had MRIs at both baseline and 10-year follow-up (n=481) (Figure 1).

Bone-Marrow Lesions (mm^2)

Subchondral BMLs were assessed on T2-weighted MRIs using OsiriX software at medial and lateral sites of tibia and femur. BMLs were defined as areas of increased signal intensity on T2-weighted images, located immediately under the articular cartilage. One trained observer read the BMLs with the images paired and the chronological order known, by measuring the maximum area of the lesion at each site at baseline (n=661) and 10-year follow-up (n=496) (Figure 1). Intra-observer reliability was excellent (0.98 (95% CI; 0.96, 0.99)).

Primary total knee replacement

Incident primary (first-time) TKR was determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), between 1 March 2002 and 21 September 2016. AOANJRR collects data from both public and private hospitals[20] in Tasmania. Matched data obtained from AOANJRR included the date and side of TKR, primary or revision TKR and the reason for TKR (e.g.: OA)[7]. In this cohort, there were 3 uni-compartmental knee replacements (Figure 1).

Ambulatory activity

AA was determined as steps/day using pedometers (Omron HJ–003 & HJ-102, Omron Healthcare, Kyoto, Japan), at baseline. The participants were informed on pedometer use, keeping a log/diary of step-count and the time during which those were worn. They were required to wear the pedometers for seven consecutive days as they conducted day-to-day activities except during water activities and sleeping. This was repeated after six months in order to account for habitual changes in different seasons. Therefore, 2 sets of logs were available per participant. Readings were screened and excluded if there was any evidence of artificial pedometer readings. Then, pedometer wear-time was determined for each day utilizing the pedometer logs. A 'valid pedometer wear-day' was considered as a day on which the pedometer was worn for at least 8 hours. Then, the steps/day count was calculated as the mean of the two pedometer logs, with a minimum of five valid wear days[3].

Anthropometrics

Weight was measured to the nearest 0.1 kg using electronic scales (Heine, Dover, New Hampshire, USA). Height was measured to the nearest 0.1 cm using a Leicester stadiometer (Invicta, Leicester, UK). BMI (kg/m^2) was calculated.

Knee pain

Knee pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[21] which consists of five subscales, each scored on a 10-point scale ranging from 0 (no pain) to 9 (most severe pain). A total WOMAC pain score was calculated by summing the five subscales.

Comorbidities

Self-reported prevalence of common comorbidities including musculoskeletal (osteoporosis, rheumatoid arthritis), cardio-respiratory (heart attacks, hypertension, thrombosis, diabetes, asthma, bronchitis/emphysema), and other medical conditions (hyperthyroidism, hypothyroidism, other major medical conditions) were collected.

Other covariates

Information on age, smoking and alcohol consumption were collected at baseline. The participants' socio-economic status was determined by the Socio-Economic Indexes for Areas (SEIFA) defined by Australian Bureau of Statistics. History of knee injury was assessed at 2.5-year follow-up. Knee x-rays were performed at baseline for all participants and scored for

209 osteophytes and joint space narrowing[22] and prevalence of radiographic OA (ROA) was
210 defined.
211
212 **Statistical analysis**
213
214 Latent class analysis (LCA) was used to identify subgroups of participants with similar
215 characteristics considering baseline AA, WOMAC pain, BMI and prevalence of comorbidities.
216 Using the variables, LCA determines the least number of meaningful classes with minimized
217 within-class and maximised between-class variation and calculates the likelihood of each
218 participant being allocated to a class[23].
219
220 In order to identify the optimum number of classes that meaningfully group participants with
221 similar characteristics, several model fit statistics including log-likelihood (LL), Akaike
222 information criterion (AIC) and Bayesian information criterion (BIC) were used in
223 combination[24]. Then a model with higher LL and lower AIC, BIC was identified.
224 Additionally, the overall model interpretability was considered in identifying the number of
225 classes[25, 26]. Furthermore, predictions of the maximum posterior probability of class
226 membership were used to evaluate an individual's probability of being in each class[25].
227
228 Baseline characteristics of the population by subgroups were described as means and standard
229 deviations or as percentages as appropriate.
230
231 The association between the subgroups and the 10-year cartilage volume change was estimated
232 using linear mixed-effects models. The model included fixed-effects terms for time (years),
233 subgroup, and a subgroup by time interaction. The interaction term estimates the cartilage

volume change per year over the period for each subgroup compared to the reference group (subgroup 1). A random intercept was specified for each participant to account for baseline individual differences.

Log-binomial regression was used to estimate the association between the subgroups and worsening BMLs which was defined as the incidence of a deleterious change in BML area representing a genuine change of BMLs. A deleterious change in BMLs was determined as an increase of BML size larger than the least significant criterion ($52mm^2$); this considers the measurement error and the correlation between the BML measurements at both baseline and 10-year follow-up[18, 27].

Log-binomial regression using a generalized estimating equation with log link and binomial family was used to estimate the relationship between the subgroups and risk of TKR. In order to account for the correlation between observations on the same individual (right and left legs), an exchangeable correlation structure was used adjusting for standard errors using the sandwich (robust) estimator of variance[28].

All the models were adjusted for baseline age, sex and knee injury. Since knee ROA is an important indication for TKR[29], we additionally adjusted the TKR model for baseline ROA in order to assess if the relationships were independent of ROA. Other potential confounders were considered but were not included in the final models as they did not change the relative risk (RR) or beta-coefficients by at least 10%[30].

Effect modification of cartilage volume change for subgroups was explored using 3-way interaction terms (and their respective lower order terms) with age, sex and knee injury. For

worsening BMLs and the risk of TKR, effect modification was explored using two-way interactions for subgroups with age, sex, knee injury and ROA.

To address any potential bias due to missing data, we conducted sensitivity analyses using inverse probability weighting, assuming that the data were missing at random (MAR)[31, 32]. This was done under two steps; first, the probability of a participant being present at the follow-up was estimated by fitting logistic regression models using baseline variables (age, sex, BMI, comorbidities, socio-economic status, AA, smoking and alcohol consumption), second, the models estimating the associations were weighted using the inverse of the estimated probabilities of being present at the follow-up.

A p value less than 0.05 (two-tailed) was regarded as statistically significant. All statistical analyses were performed on Intercooled Stata V.15.1 for Mac (StataCorp LP, Texas, USA).

RESULTS

The average follow-up period for cartilage volume change and BMLs was 10.7 years (±0.7), while for TKR, it was 12.1 years (±2.8). 1049 participants were included in the LCA models.

Subgroup identification

LCA model fit statistics were assessed for two to six classes. Although the LL was slightly higher for a two-class model, compared to a three-class model (-5578 vs. -5563), the AIC and BIC all favoured the three-class model with lower AIC and BIC, compared to two-class model (AIC, 11160 vs. 11183; BIC, 11245 vs. 11248). Between three-class and four-class models, a three-class model was favoured owing to higher LL (-5563 vs. -5560), lower AIC (11160 vs. 11161) and lower BIC (11245 vs. 11261). Comparing with five- and six-class models, a three-class model was favoured as the LL was higher and BIC was lower although AIC was slightly higher (Supplementary table 1). Furthermore, five- or six-class models did not suggest distinctive classes in comparison to the more parsimonious three-class model . Hence the three-class model was considered as the best fit. Once the class structure was determined, the participants were allocated to the classes based on the predictions of the maximum posterior probability. The mean posterior probability for the three classes were 0.78 (±0.19), 0.75 (±0.15) and 0.70 (±0.11).

Three classes/subgroups were identified: subgroup 1 (43%): Normal/overweight participants with higher AA levels, lower pain and lower prevalence of comorbidities; subgroup 2 (32%): Overweight participants with lower AA levels, mild pain and higher prevalence of

297 comorbidities; subgroup 3 (25%): Obese participants with lower AA levels, mild pain and
298 higher prevalence of comorbidities.

299

300 **Baseline characteristics**

301

302 Compared to subgroup 1, participants in subgroup 2 and 3 were older, had lower AA levels,
303 higher BMI, higher WOMAC pain (although their pain was in the mild range), a higher
304 prevalence of comorbidities and a higher prevalence of knee ROA (Table 1).

305

306 Participants with missing data were older and had lower AA levels. They were also more likely
307 to have higher WOMAC pain and higher prevalence of comorbidities (Supplementary table 2).

308

309 **Association of subgroups and the change in tibial cartilage volume**

310

311 The mean cartilage volume loss of the population over 10 years was 465 (±231) mm^3 (data not
312 shown). On average, cartilage volume for subgroup 1 decreased by 256.70 mm^3 (95% CI -
313 354.35, -159.05) over 10 years. Multivariable analyses showed that participants in subgroup 3
314 had greater cartilage volume loss over 10 years while subgroup 2 was not associated with
315 cartilage volume change, compared to subgroup 1 (Table 2).

316

317 **Association of subgroups and worsening BMLs**

318

There were 221/489 participants with worsening BMLs over 10 years. In multivariable analyses, being in subgroup 2 or 3 was not associated with worsening BMLs, compared to subgroup 1 (Table 3).

Association between subgroups with the risk of TKR

There were 79/899 participants with a TKR. Multivariable analyses showed that participants in subgroup 3 had a greater risk of TKR while subgroup 2 was not associated with a risk of TKR, compared to subgroup 1 (Table 4).

There was no evidence for interaction by age, sex, knee injury or ROA in any of the models.

The results of the sensitivity analyses that used inverse probability weighting were similar with no changes to the inference when compared to the complete case analysis (Supplementary tables 3–5).

DISCUSSION

This prospective cohort study identified subgroups of participants with similar characteristics in a population of community-dwelling older-adults and assessed the longitudinal association of these subgroups with cartilage volume change, worsening BMLs and TKR. Three subgroups were identified; subgroup 1: Normal/overweight participants with higher AA, lower pain, and lower prevalence of comorbidities; subgroup 2: Overweight participants with lower AA, mild pain and higher prevalence of comorbidities; subgroup 3: Obese participants with lower AA, mild pain and higher prevalence of comorbidities. We found that subgroup 3 participants lost more cartilage volume and were at a higher risk of TKR, while being in subgroup 2 was not associated with knee OA outcomes, compared to subgroup 1. These findings suggest the existence of subgroups of participants within a population and highlight the importance of identifying characteristic/risk factor patterns that may cluster together and using them to determine subgroups of people who may be at a higher risk of developing and progressing OA.

There has been increasing interest in the field of OA research to identify clinical phenotypes/subtypes of OA, based on clinical, imaging and laboratory biomarkers[12, 25, 33-35]. Individual biomarkers are not adequate in defining disease onset or progression[13]; therefore, determining clinical subtypes of OA presents advantages in accurate treatment allocation and development of new treatment strategies. It is equally important to identify subgroups of participants that may carry a higher risk for the development and progression of OA which would also be helpful to define tailored strategies to prevent or slow the disease progression[36]. To the best of our knowledge, no other studies have evaluated the existence of subgroups with relatively homogenous characteristics related to AA. Taken together, these studies further substantiate the existence of homogenous subgroups within populations and the

utility of classifying subgroups within a cohort, to better identify participants at a higher risk of OA development and progression.

Interestingly, AA has been shown to be beneficial for symptomatic knee OA and is widely used as a treatment in relieving symptoms[37]. Yet, the beneficial or harmful effects of AA on structural development and progression of OA remains uncertain[3]. Hence, studying the clustered effects of AA with other characteristics/risk factors may be important and provides a novel strategy to help unravel the AA and OA debate. The healthy subgroup (subgroup 1) observed in this study with normal BMI, *higher AA*, lower pain and lower prevalence of comorbidities, did not appear to have an increased risk of cartilage volume loss, worsening BMLs or incident TKR, compared to other subgroups (data not shown). Hence it may be argued that, amidst other characteristics/risk factors, AA may not be a factor that contributes substantially to the increased risk of structural progression in OA. However, due to the nature of this analysis, it is difficult to separate the independent effects of AA on the outcomes, hence further studies are needed to confirm this hypothesis.

In this study, subgroup 3 participants lost more cartilage volume and were at an increased risk of TKR, compared to subgroup 1. Studies have shown that obesity is associated with increased cartilage volume loss[38] and increased risk of TKR[7], owing to the increased loading and low-grade inflammation[5]. Additionally, in previous studies conducted on this cohort, authors found that AA was not related to cartilage volume loss as a main effect[3], but was associated with a small increased risk of TKR[7]. Furthermore, higher prevalence of comorbidities and higher pain may co-occur with higher BMI and lower AA, suggesting that these factors may have complex interplay which leads to early expression of the underlying disease processes related to OA. Interestingly, subgroup 3 was not related with worsening BMLs. Previous

reports have shown that BMI was not associated with worsening BMLs[18, 39, 40], while AA has been suggested to be related with an increased risk of worsening BMLs[3]. Therefore, it may be that worsening of BMLs is a result of several contributing factors. Subgroup 2 was not associated with any OA outcome. Indeed, the majority of the participants in this cohort were overweight older-adults. Although there were statistically significant differences in BMI between the subgroups 1 and 2, it was only a little higher in subgroup 2, compared to subgroup 1. Hence, the smaller increase in BMI combined with other characteristics/risk factors may not contribute to the risk of long-term OA outcomes for subgroup 2.

It is further important to consider why these subgroups can be defined using these variables in this cohort. Both physiological and environmental factors may play a key role in determining these subgroups. Subgroup 1 represents participants with mostly normal/overweight BMI, higher AA, lower pain and comorbidities who were younger compared to the other subgroups; hence, signifies a younger, active and healthy group. Subgroup 2 was largely comprised of overweight participants with lower AA, mild pain and higher comorbidity levels and the participants were older compared to the other subgroups. The prevalence of higher comorbidity levels, mild pain and older age may partly explain their lower AA levels[10, 15, 41, 42]. In subgroup 3, participants were mainly obese with lower AA, mild pain and higher comorbidity levels, representing a group with mechanical overloading and metabolic syndrome[34]. In line with this, a recent systematic review suggested six clinical phenotypes out of which three included a higher BMI/obesity component, characterized by inflammatory mechanisms, metabolic syndrome and mechanical overloading[11]. Furthermore, a higher prevalence of comorbidities in the subgroups 2 & 3 may be suggestive of ongoing, widespread systemic inflammation[43]. Importantly, the findings of this study may be used in clinical settings to guide treatment allocation for older-adults. Weight loss programs with increased AA/exercise,

prevention or management of comorbidities and pain may be recommended in clinical settings for people who demonstrate characteristics similar to subgroup 3. Those who express subgroup 2 characteristics may benefit from weight maintenance/loss with increased AA/exercise, prevention or management of comorbidities and pain.

There are a few strengths to this study that includes the long-term follow-up, community-based cohort, large sample size, inclusion of objectively measured and validated exposure (AA, BMI and pain) and outcome (cartilage volume, BMLs, TKR) measures. This study used an LCA approach to define subgroups where methods such as LCA or cluster analysis are more reliable, less subjective and appropriate methods in defining naturally occurring subgroups in a population[13, 44]. However, there are a few limitations to this study. First, while LCA is a suggested method, it largely depends on the choice of variables. Yet, in this analysis, we have mostly used objective and standardized variables to define subgroups. Second, there can be differences in AA participation in different ethnic groups[45]. This cohort was largely comprised of Caucasians, therefore, these subgroups may not be directly applicable to other populations, which hinders the generalizability. Hence, further studies exploring the subgroups in other populations/ethnic groups are warranted. Third, in this study, subgrouping was only performed at baseline, and potential temporal changes of the characteristics and their implications were not assessed. Fourth, we have only considered activity during ambulation, and have not considered the intensity or nature of the activity, due to the lack of information. Fifth, there were missing data in the analyses, and the participants with missing data were older and had lower AA levels. However, in the sensitivity analyses, we observed that, although the effect sizes were slightly different, the inference was not changed when compared to the complete case analysis. This suggests that there was no bias introduced to the final results of the complete case analysis by the missing data.

In summary, the findings of this study suggest the existence of homogeneous subgroups of participants and support the utility of identifying patterns of characteristics/risk factors that may cluster together and using them to identify subgroups of people who may be at a higher risk of developing and/or progressing OA.

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AUTHORS ROLES/CONTRIBUTORS

Ishanka P. Munugoda was responsible for data acquisition, management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and completed manuscript revisions and the final draft. Feng Pan and Karen Wills participated in analysis and interpretation of the data, and critically revised the manuscript. Flavia Cicuttini designed and carried out the study planning, participated in analysis and interpretation of the data, and critically revised the manuscript. Siti M. Mattap, Stephen E. Graves and Michelle Lorimer helped in data collection, participated in interpretation of the data, and critically revised the manuscript. Graeme Jones designed and carried out the study planning, participated in analysis and interpretation of the data, and critically revised the manuscript. Michele L. Callisaya designed and carried out the study planning, participated in analysis and interpretation of the data and critically revised the manuscript. Dawn Aitken designed and carried out the study planning, helped in data management, participated in analysis and interpretation of the data, assisted with the initial manuscript draft, and critically revised the manuscript. All authors have approved the final manuscript.

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CONFLICT OF INTERESTS

G. Jones has received consulting fees and payments for lectures from multiple pharmaceutical companies. However, no institution/company funded or had any input at any stage of the conduct of this study, data analysis or writing of the manuscript. Other authors declare no conflicts of interests.

PATIENT CONSENT

Obtained.

ETHICS CONSIDERATIONS

The research was conducted in compliance with the Helsinki Declaration. Ethical approval was granted by the Southern Tasmanian Health and Medical Human Research Ethics Committee. Written informed consent was obtained from all participants.

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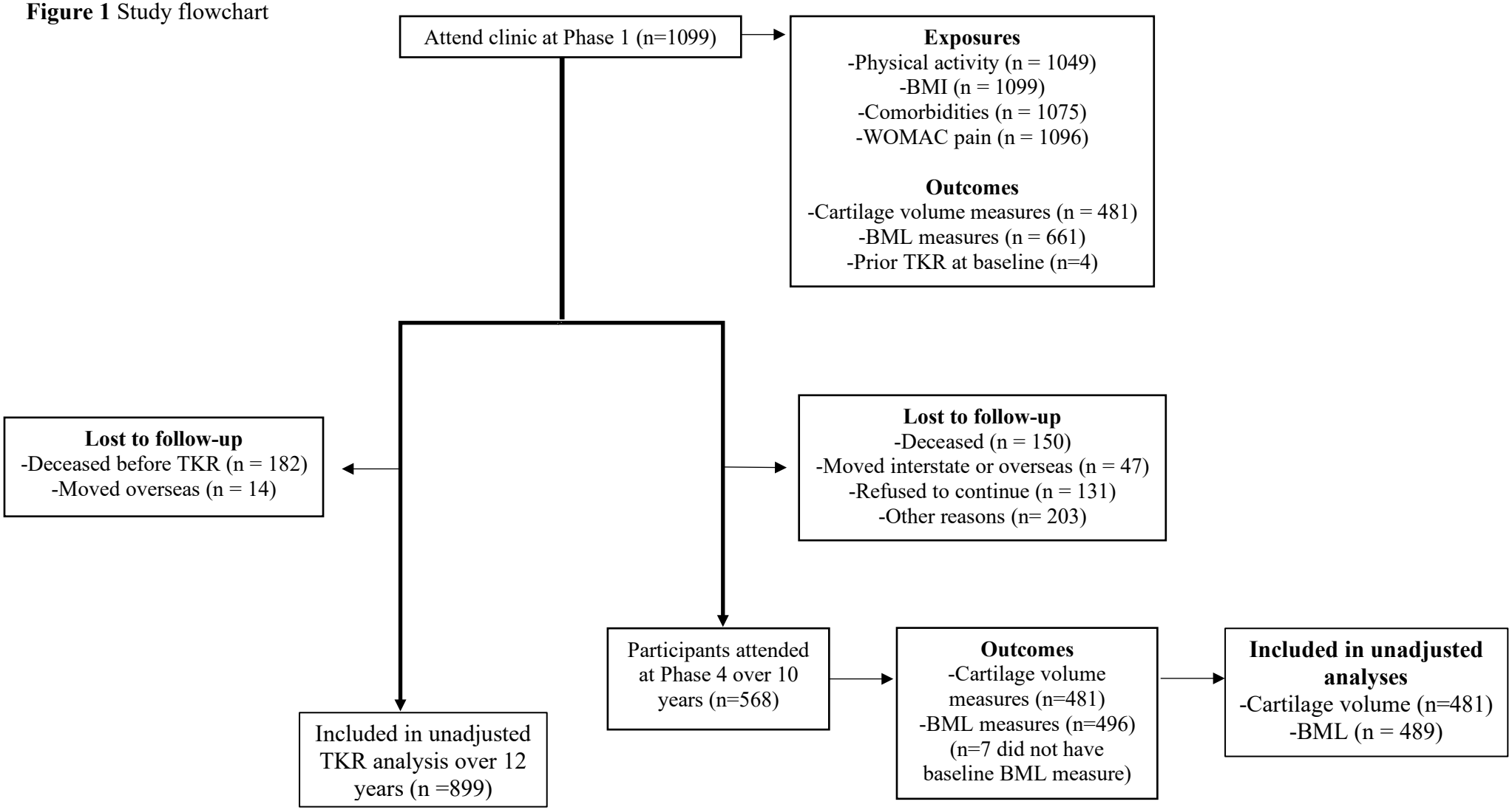
Figure 1 Study flowchart



BMI – body mass index, WOMAC - Western Ontario McMaster Osteoarthritis Index, BML – bone marrow lesions, TKR – total knee replacement.

Table 1 Baseline characteristics of the 3 subgroups

	Subgroup 1 (n=451; 43%) Mean (SD)	Subgroup 2 (n=340; 32%) Mean (SD)	Subgroup 3 (n=258; 25%) Mean (SD)	Total sample (n=1049) Mean (SD)
Age (years)	**60.9 (6.7)**	**65.8 (7.7)**	**62.7 (7.1)**	62.9 (7.4)
Sex (Female: %)	49	49	57	51
Ambulatory activity (steps/day)	**10,780 (3,006)**	**6,879 (2,343)**	**7,117 (2,891)**	8,615 (3,355)
BMI (kg/m^2)	**25.5 (3.0)**	**26.1 (2.5)**	**34.1 (3.7)**	27.8 (4.7)
BMI categories				
Normal/Underweight (%)	**44**	**30**	**0**	29
Overweight (%)	**50**	**70**	**0**	44
Obese I (%)	**6**	**0**	**69**	19
Obese II & above (%)	**0**	**0**	**31**	8
WOMAC pain	**2.1 (4.2)**	**4 (6.0)**	**5.8 (8.0)**	3.6 (6.1)
Comorbidities (%)	**49**	**96**	**86**	73
Knee ROA (%)	**55**	**63**	**66**	60

643 BMI – body mass index, WOMAC - Western Ontario McMaster Osteoarthritis Index, ROA - Radiographic osteoarthritis.

644 Significant between-group differences shown in bold.

Table 2 Association between subgroups and the cartilage volume change over 10 years

	Unadjusted (n=481)		†Adjusted (n=481)	
	*β	(95% CI)	*β	(95% CI)
Mean change for subgroup 1 over 10 years (mm^3)	-414.96	(-439.32 -390.60)	-256.70	(-354.35, -159.05)
Change in cartilage volume for each subgroup over 10 years*				
Subgroup 1 (n = 259)	Ref		Ref	
Subgroup 2 (n = 116)	13.21	(-30.84, 57.25)	13.06	(-30.87, 57.00)
Subgroup 3 (n = 106)	**-66.46**	**(-111.79, -21.13)**	**-60.56**	**(-105.91, -15.21)**

†Adjusted for age, sex and history of knee injury. Significant results shown in bold, *β-coefficient represents the difference in cartilage volume change for each subgroup compared to subgroup 1, over 10 years.

649 **Table 3** Association between subgroups with worsening bone-marrow lesions over 10 years

	Unadjusted (n=489)		†Adjusted (n=488)	
	RR	(95% CI)	RR	(95% CI)
Subgroup 1 (n = 257)	Ref		Ref	
Subgroup 2 (n = 124)	0.91	(0.71, 1.16)	0.93	(0.72, 1.19)
Subgroup 3 (n = 108)	0.99	(0.78, 1.27)	1.02	(0.80, 1.30)

650 †Adjusted for age, sex and history of knee injury.

Table 4 Association between subgroups with the risk of total knee replacements over 12 years

	Unadjusted (n=899)		†Adjusted (n=687)	
	RR	(95% CI)	RR	(95% CI)
Subgroup 1 (n = 417)	Ref		Ref	
Subgroup 2 (n = 260)	1.17	(0.64, 2.15)	1.16	(0.56, 2.36)
Subgroup 3 (n = 222)	**2.77**	**(1.67, 4.58)**	**3.19**	**(1.75, 5.81)**

†Adjusted for age, sex, history of knee injury and knee radiographic OA. Significant results are shown in bold.